Table 1. A Simple Gene-Environment Interaction Model in the Context of Epidemiologic Studies

Cohort Study				Case-control study		
Exposure (1=present, 0=absent)	**Susceptibility Genotype**	**Disease Risk**	**Relative Risk**	**Cases**	**Controls**	**Odds Ratio**
0	0	I	1	A_{00}	B_{00}	1
0	1	IR_g	R_g	A_{01}	B_{01}	$R_g=A_{01}B_{00}/A_{00}B_{01}$
1	0	IR_e	R_e	A_{10}	B_{10}	$R_e=A_{10}B_{00}/A_{00}B_{10}$
1	1	IR_{ge}	R_{ge}	A_{11}	B_{11}	$R_{ge}=A_{11}B_{00}/A_{00}B_{11}$

I refers to the background disease risk, incidence of disease among members of the cohort
who are not exposed to the environmental factor and who are genotype negative.
R_e = disease risk among persons with the exposure without the genotype divided by disease risk among persons with no exposure and no susceptible genotype.
R_g = disease risk among persons with the genotype without the exposure divided by disease risk among persons with no exposure and no susceptible genotype.
R_{ge} = disease risk among persons with the exposure and genetype divided by disease risk among persons with no exposure and no susceptible genotype.

Table 2. Six Patterns of Gene-Environment Interaction

Patterns	Effects on Disease: Genotype in absence of environment	Risk of: Environment in absence of genotype
1	No effect $R_g = 1$	No effect $R_e = 1$
2	No effect $R_g = 1$	Increase risk $R_e > 1$
3	Increase risk $R_g > 1$	No effect $R_e = 1$
4	Increase risk $R_g > 1$	Increase risk $R_e > 1$
5	Decrease risk $R_g < 1$	No effect $R_e = 1$
6	Decrease risk $R_g < 1$	Increase risk $R_e > 1$

Source: Khoury et al. 1993 (24).

R_e = disease risk among persons with the exposure without the genotype divided by disease risk among persons with no exposure and no susceptible genotype.
R_g = disease risk among persons with the genotype without the exposure divided by disease risk among persons with no exposure and no susceptible genotype.

Table 3. Parameters of Gene-Environment Interaction Analysis in a Case-Control Design

Exposure	Susceptibility Genotype	Cases	Controls	Odds Ratio
-	-	$\frac{(1-g)(1-e)}{3}$	(1-g)(1-e)	1.0
-	+	$\frac{g(1-e)R_g}{3}$	g(1-e)	R_g
+	-	$\frac{e(1-g)R_e}{3}$	e(1-g)	R_e
+	+	$\frac{geR_{ge}}{3}$	ge	R_{ge}

e = prevalence of exposure in the population.
g = prevalence of genotype in the population.
R_e = disease risk among persons with the exposure without the genotype divided by disease risk among persons with no exposure and no susceptible genotype.
R_g = disease risk among persons with the genotype without the exposure divided by disease risk among persons with no exposure and no susceptible genotype.
R_{ge} = disease risk among persons with the exposure and genetype divided by disease risk among persons with no exposure and no susceptible genotype.

$3 = (1-g)(1-e) + g(1-e)R_g + e(1-g)R_e + geR_{ge}$

Table 4. Characteristics of Case-Only, Case-Parental and Affected Sib-pair Studies

Feature	Case-Only	Case-Parental Control	Affected Relative-Pair
Study subjects	Cases	Cases and their parents	Proband, second case in family, and parents
'Controls'	None	Expected genotype distribution based on parental genotypes	Expected distribution of alleles with Mendelian transmission
Assessment	Departure from multiplicative relationship between exposure and genotype	Association between genotype and disease	Linkage between locus and disease
Assumptions	Independence between genotype and exposure	Mendelian transmission	Mendelian transmission
Limitations	Cannot assess effects of exposure on genotype. Linkage disequilibrium.	Requires one or both parents. Cannot assess exposure effects. Linkage disequilibrium.	Need families with 2 or more cases. Cannot assess exposure. Cannot assess specific alleles.

Source: Khoury, 1997 (1)

Table 5. Gene-Environment Interaction Analysis in the Context of a Case-Only Study

Exposure	Susceptibility	Genotype
	-	+
-	a	b
+	c	d

a = ((1-g)(1-e)) / 3
b = ((1-g)eR_e) / 3
c = ((1-e)gR_g) / 3
d = (geR_{ge}) / 3

e = prevalence of exposure in the population.
g = prevalence of genotype in the population.
R_e = disease risk among persons with the exposure without the genotype divided by disease risk among persons with no exposure and no susceptible genotype.
R_g = disease risk among persons with the genotype without the exposure divided by disease risk among persons with no exposure and no susceptible genotype.
R_{ge} = disease risk among persons with the exposure and genetype divided by disease risk among persons with no exposure and no susceptible genotype.

3 = (1-g)(1-e) + g(1-e)R_g + e(1-g)R_e +geR_{ge}

Under assumption of independence between exposure and genotype among controls: case-only odds ratio (OR_{ca})= ad/bc. OR_{ca} is related to case-control ORs by $OR_{ca} = R_{ge}/(R_e*R_g)$.

Table 6. Case-Control Analysis of the Interaction Between Maternal Cigarette Smoking and Transforming Growth Factor Alpha Polymorphism in Determining Children's Risk for Cleft Palate

Smoking	TaqI Polymorphism	Cases	Controls	Odds Ratio	95% C.I.
-	-	36	167	1.0	Referent
-	+	7	34	1.0	0.3-2.4
+	-	13	69	0.9	0.4-1.8
+	+	13	11	5.5	2.1-14.6

Sources: it is derived from Hwang et al. (42).
Odds ratio based on a case-only study is 5.1 (95% CI 1.5-18.5)(36 * 13)/(13 * 7).

Table 7. Gene-Environment Interaction Analysis in the Context of a Case-Parental Control Study: Analysis of Nontransmitted Alleles

Exposure status: Absent		**Case genotype**	
		S	+
Parental non-transmitted alleles	-	T_0	U_0
	+	V_0	W_0
OR among unexposed people		1	U_0/V_0

Exposure status: Present		**Case genotype**	
		S	+
Parental non-transmitted alleles	-	T_1	U_1
	+	V_1	W_1
OR among exposed people		1	U_1/V_1

Source: Khoury and Flanders, 1996 (34).

Table 8. Gene-Environment Interaction Analysis in the Context of an Affected Sib-Pair Study

No. Alleles ibd with proband	**Unexposed case**	**Exposed case**	**Expected**	**Odds Ratio** (unexposed)	**Odds Ratio** (exposed)
0	A_{00}	A_{01}	0.25	1.0	1.0
1	A_{10}	A_{11}	0.50	$A_{10}/2A_{00}$	$A_{11}/2A_{01}$
2	A_{20}	A_{21}	0.25	A_{20}/A_{00} A_{21}/A_{01}	

Source: Khoury, 1997 (1).